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A Review On Study & Treatment Of Cyanocobalamin (Vitamin B12)

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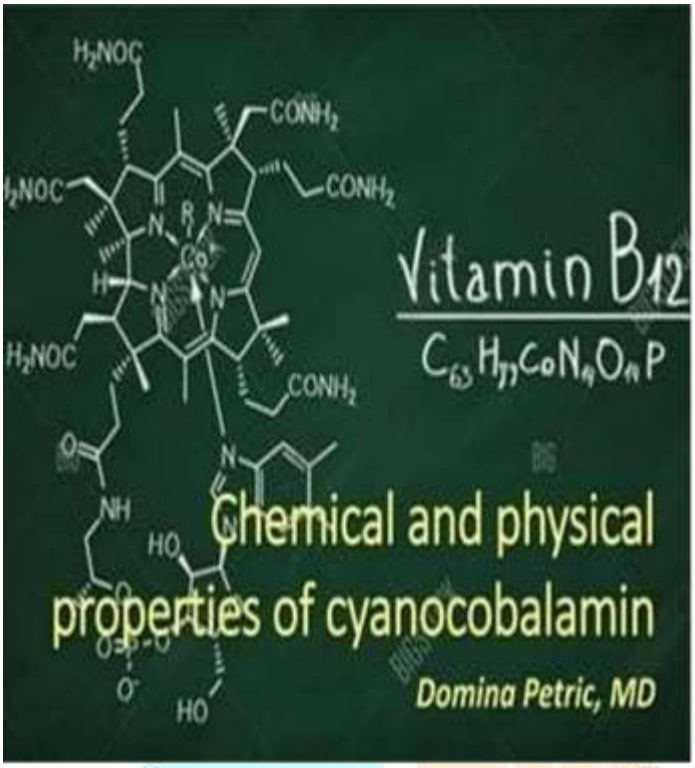
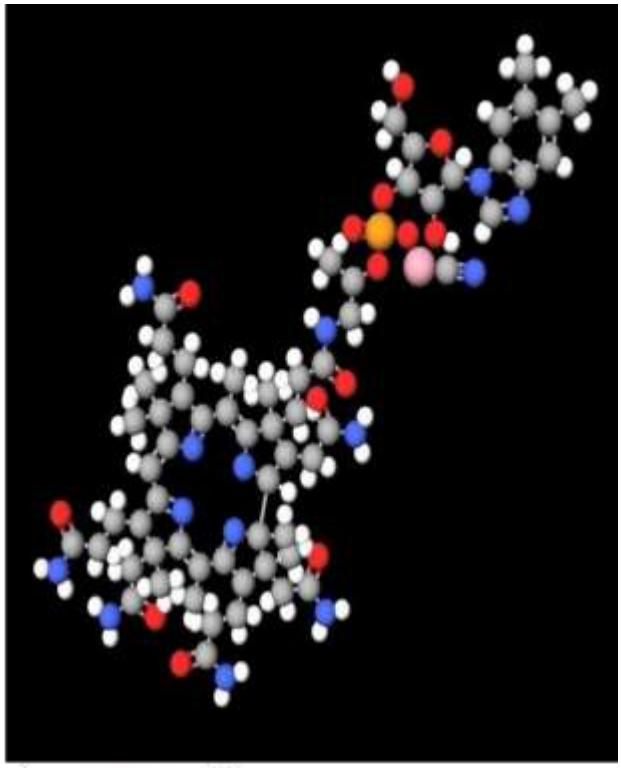
Abstract:

Vitamin B12 deficiency in early childhood is an important cause of neurodevelopmental delay and regression. Most of these cases occur in exclusively breast-fed infants of deficient mothers. Symptoms and signs of vitamin B12 deficiency appear between the ages of 2 to 12 months and include vomiting, lethargy, failure to thrive, hypotonia, and arrest or regression of developmental skills. Approximately one half of this cases exhibit abnormal movements, variously described as tremors, twitches, chorea, or myoclonus. Urinary concentrations of methylmalonic acid and homocysteine are characteristically elevated in vitamin B12 deficiency. Hyperglycosuria is sometimes present. The early diagnosis and treatment of vitamin B12 deficiency is crucial for significant neurological impairment and long-term prognosis. Treatment with vitamin B12 corrects these metabolic abnormalities very rapidly (within a few days). Vitamin B12 supplementation of pregnant women may prevent neurological and neuroradiological findings of the infants. Because of the importance of vitamin B12 in the development of the foetal and neonatal brain, vegetarian and vegan mothers should be aware of the severe and not fully-reversible damages caused by insufficient nutritional intake of vitamin B12 during pregnancy and lactation. Therefore, efforts should be directed to prevent its deficiency in pregnant and breastfeeding women on vegan diets and their infants. It is also important to take the nutritional history of both infants and their mothers for the early prevention and treatment. Here an interesting case of vitamin B12 deficiency in a 10-monthold boy presented with psychomotor regression, hypotonia and lethargy.

Keywords: Vitamin B12 deficiency; breastfeeding; case report; pallor; psychomotor regression.





Introduction:

Cyanocobalamin is a medication used to manage and treat vitamin B12 deficiencies. Chemically it belongs to a class called "coronoids," and it is a crystallizable cobalt complex. The name cyanocobalamin derives from the cyanide group attached to the molecule. This activity reviews the indications, action, and contraindications for cyanocobalamin as a valuable agent in managing vitamin B12 deficiencies and other off-label uses (and other applicable disorders).

In addition, this activity will highlight the mechanism of action, adverse event profile, and other key factors (e.g., off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, relevant interactions) pertinent for members of the interprofessional team in the care of patients with such conditions.

Cyanocobalamin is a form of vitamin B12 used to treat and prevent vitamin B12 deficiency except in the presence of cyanide toxicity. The deficiency may occur in pernicious anaemia, following surgical removal of the stomach, with fish tapeworm, or due to bowel cancer. It is used by mouth, by injection into a muscle, or as a nasal spray.

Literature review:

- *Biochemical, Nutritional, and Clinical Parameters of Vitamin B12 Deficiency in Infants: A Systematic Review and Analysis of 292 Cases Published between 1962 and 2022.*
- *Winterson M, et al. Nutrients. 2023. PMID: 38068819 Free PMC article. Review.*
- *Psychomotor regression due to vitamin B12 deficiency.*
- *Bosselated A, et al. Pan Afra Med J. 2018. PMID: 30374398 Free PMC article.*
- *[Metabolic complications and neurologic manifestations of vitamin B12 deficiency in children of vegetarian mothers].*
- *Smolka V, et al. Cas Lek Cesk. 2001. PMID: 11787236 Czech.*
- *Severe vitamin B12 deficiency in an exclusively breastfed 5month-old Italian infant born to a mother receiving multivitamin supplementation during pregnancy.*
- *Guez S, et al. BMC Podiatry. 2012. PMID: 22726312 Free PMC article.*
- *Neurology of Nutritional Vitamin B12 Deficiency in Infants: Case Series from India and Literature Review.*
- *Goraya JS, et al. J Child Neurol. 2015. PMID: 25953825 Review.*

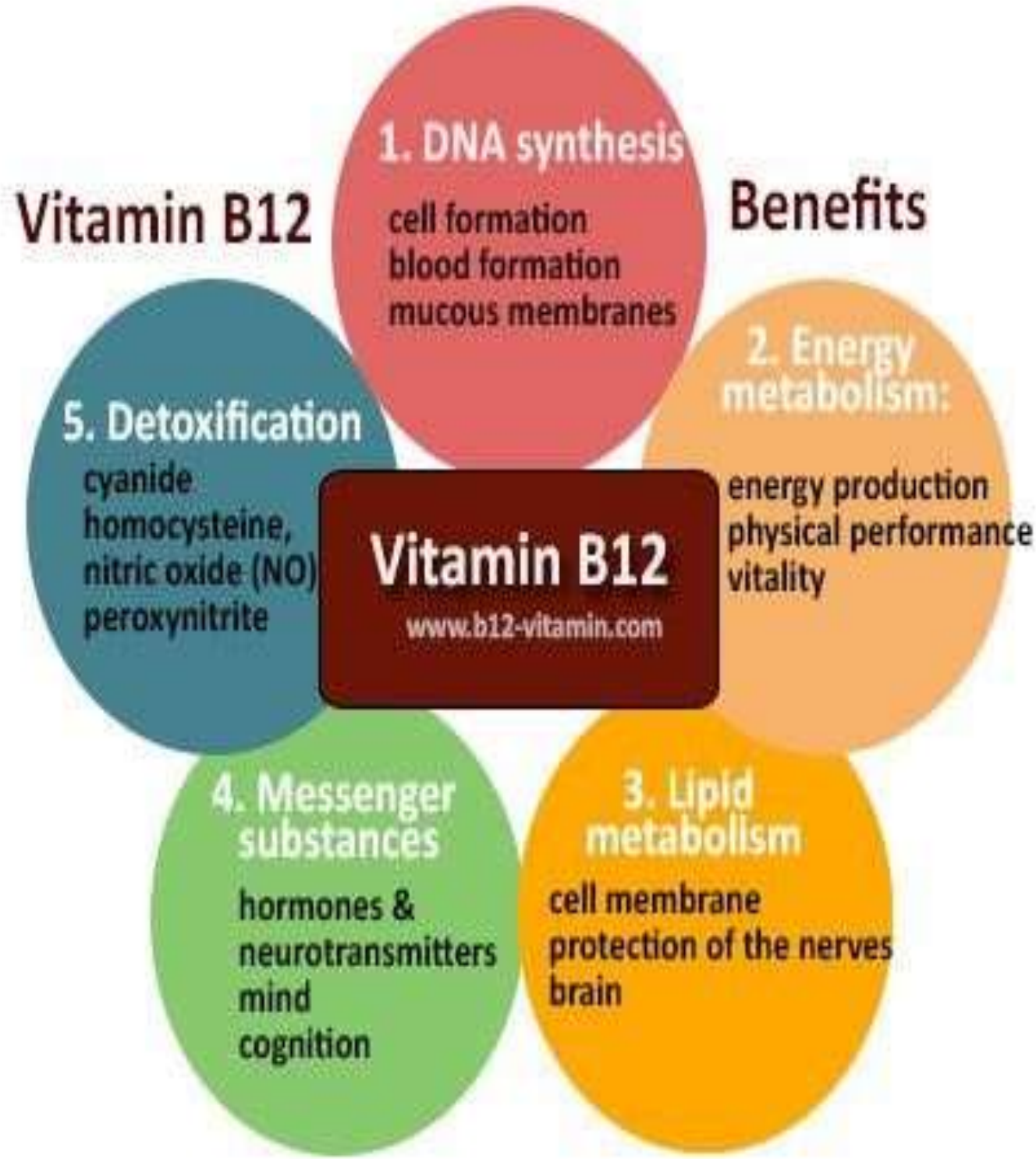


Fig. Benefits of Vitamin B12

What is Vitamin B12?

Vitamin B12 deficiency happens if you are not eating enough vitamin B12 or your body is not absorbing the vitamin B12 you consume properly.

Vitamin B12 (cobalamin) is essential for the health of nerve tissue, brain function, and red blood cells. Sources include meat, eggs, and some yeast products. People with a B12 deficiency may need supplements. Signs of a deficiency include headaches and fatigue.

Vitamin B12 is a water-soluble of any excess or unwanted vitamin B12 in the urine.

Vitamin B12 is the largest and most structurally complicated vitamin. It occurs naturally in animal products like meat and eggs, and manufacturers can produce it through bacterial fermentation synthesis.

Situations or conditions that can cause:

Vitamin B12 deficiency include: Lack of vitamin B12 in your diet: People who don't eat enough foods that naturally have vitamin B12 or don't eat foods fortified with vitamin B12 can develop vitamin B12 deficiency.

SYMPTOMS:

- Rapid breathing or shortness of breath.
- Headaches.
- Indigestion.
- Loss of appetite.
- Palpitations.
- Problems with your vision.
- Feeling weak or tired.
- Diarrhoea.

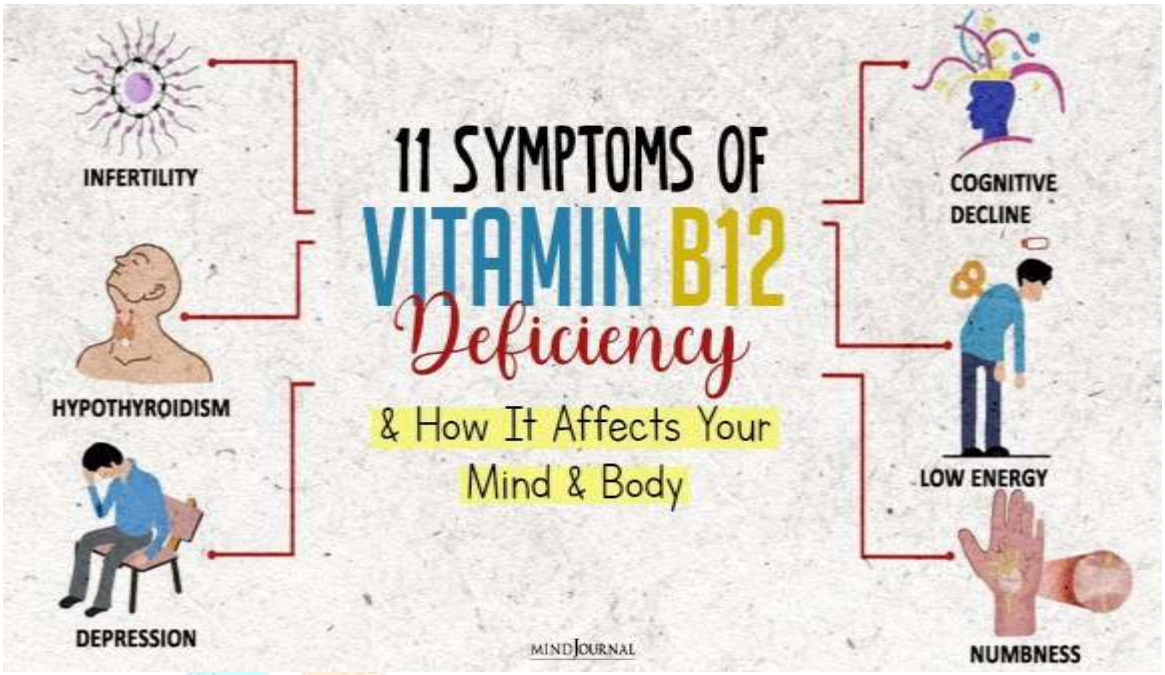


Fig. Symptoms of Vitamin B12

- **Deficiency of Vitamin B12:**

Vitamin B_{12} deficiency can potentially cause severe and irreversible damage, especially to the brain and nervous system. Deficiency at levels only slightly lower than normal can cause a range of symptoms such as fatigue, feeling weak, light-headedness, dizziness, breathlessness, headaches, mouth ulcers, upset stomach, decreased appetite, difficulty walking (staggering balance problems), muscle weakness, depression, poor memory, poor reflexes, confusion, and pale skin, feeling abnormal sensations, among others, especially in people over age 60. Vitamin B_{12} deficiency can also cause symptoms of mania and psychosis. Among other problems, weakened immunity, reduced fertility and interruption of blood circulation in women may occur.

The main type of vitamin B12 deficiency anomia is pernicious anaemia characterized by a triad of symptoms:

Anaemia with bone marrow promegaloblastosis (megaloblastic anomia). This is due to the inhibition of DNA synthesis (specifically purines and thymidine).

Gastrointestinal symptoms: alteration in bowel motility, such as mild diarrhoea or constipation, and loss of bladder or bowel control. These are thought to be due to defective DNA synthesis inhibiting replication in tissue sites with a high turnover of cells. This may also be due to the autoimmune attack on the parietal cells of the stomach in pernicious anomia. There is an association with gastric antral vascular ectasia (which can be referred to as watermelon stomach), and pernicious anomia.

Neurological symptoms: sensory or motor deficiencies (absent reflexes, diminished vibration or soft touch sensation) and subacute combined degeneration of the spinal cord Deficiency symptoms in children include developmental delay, regression, irritability, involuntary movements and hypotonia.

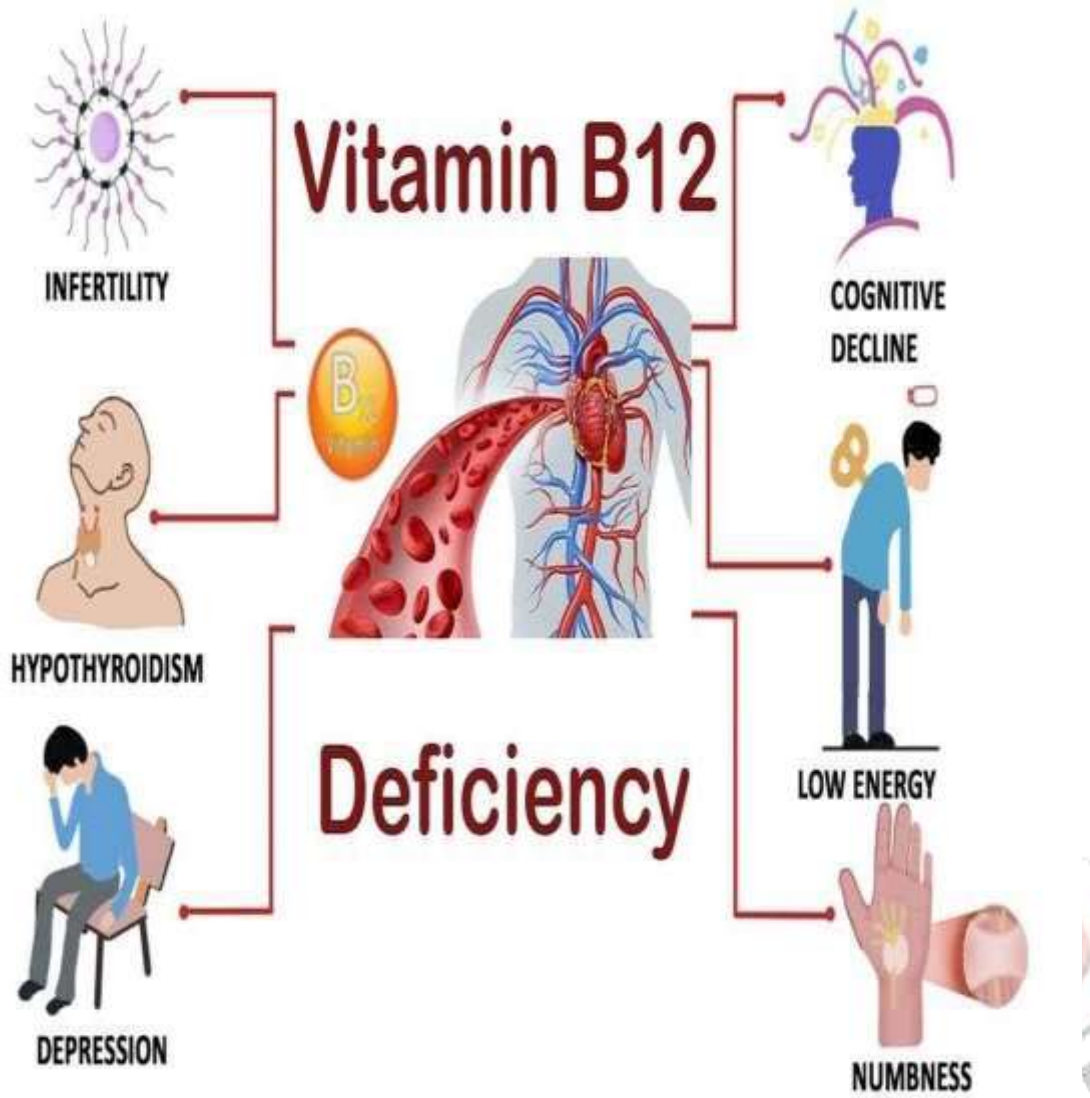


Fig. Deficiency of Vitamin B12

- **Medical Use:**

Fig. Medical Use

A vitamin B12 solution (hydroxocobalamin) in a multi-dose bottle, with a single dose drawn up into a syringe for injection. Preparations are usually bright red.

- **Treatment of deficiency:**

Severe vitamin B12 deficiency is initially corrected with daily intramuscular injections of 1000 pg. of the vitamin, followed by maintenance via monthly injections of the same amount or daily oral dosing of 1000 go. The daily dose is far in excess of the vitamin requirement because the normal transporter protein mediated absorption is absent, leaving only very inefficient intestinal passive absorption. Injection side effects include skin rash, itching, chills, fever, hot flushes, nausea and dizziness. Oral maintenance treatment avoids this problem and significantly reduces cost of treatment.

Cyanide poisoning

For cyanide poisoning, a large amount of hydroxocobalamin may be given intravenously and sometimes in combination with sodium thiosulfate. The mechanism of action is straightforward: the hydroxocobalamin hydroxide ligand is displaced by the toxic cyanide ion, and the resulting non-toxic Cyanocobalamin is excreted in urine.

Pathophysiology:

Basis on the Vitamin B12 and its absorption factors

Vitamin B12 was discovered as the antipernicious anaemia factor that was found in the liver.6–8 The discovery, by two independent teams, of liver as a dietary factor that could reverse anaemia in pernicious anaemia patients led to the Nobel prize in 1934. In the 1930s, researchers started to attempt isolating the 'active principle' in liver that contained the antipernicious anaemia factor. In the meantime, the importance of gastric juice for inducing reticulocytosis in pernicious anaemia patients was identified.

Only in 1947, two groups independently managed crystallizing the active principle. No other micronutrient than vitamin B12 is known to require a specific factor for its absorption. Without this absorption factor vitamin B12 deficiency follows. Only during the 1950s, this vitamin B12 absorption factor, called intrinsic factor (IF) as opposed to the extrinsic factor (vitamin B12 itself) had been to some extent purified.15,16 An excellent historical review of the discovery of vitamin B12 and its absorption factor has been written by Dr Kunya Okuda.

Vitamin B12 is absorbed in the small intestine where the vitamin B12–IF complex binds to a receptor. It was called coilin and found to function in the endocytosis of several ligands including the vitamin B12– IF complex and also apolipoprotein A-I and high-density lipoprotein, for example. Later the vitamin B12–IF receptor was shown to consist of two subunits coded by different genes. The second gene appeared to be coding for the protein amnion less, which is essential for gastrulation in mice. The vitamin B12–IF receptor has been called cub am. Mutations in the genes coding for either of the subunits cubilin or amnionless lead to a vitamin B12 malabsorption syndrome. This is accompanied by proteinuria, because cub am is also mediating the tubular reabsorption of protein from the primary urine.

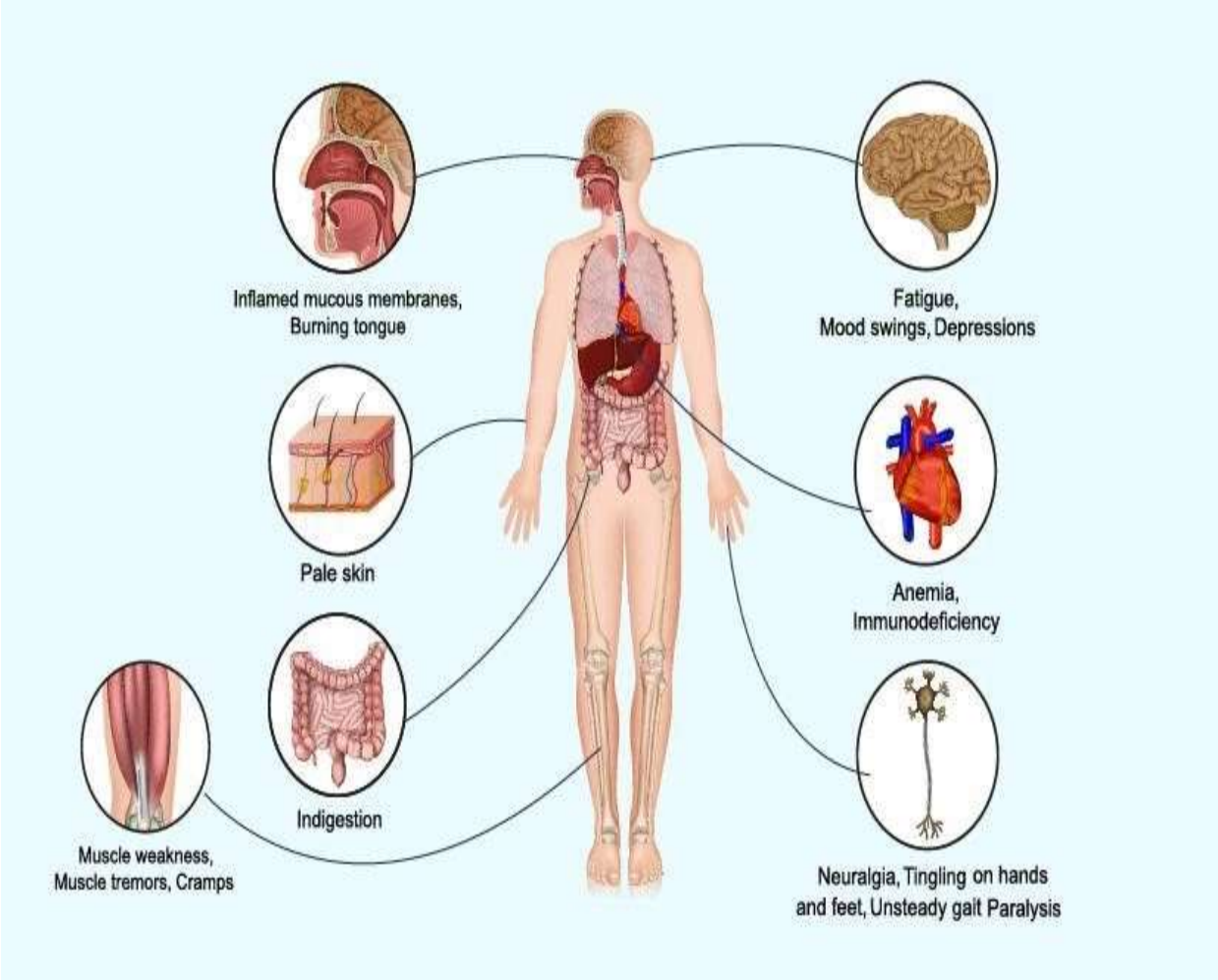


Fig. Pathophysiology

- **Metabolism of vitamin B12:**

The source of vitamin B12 in men is thus exogenous, predominantly of animal origin. However, neither fungi and plants nor animals are able to synthesize vitamin B12. Only bacteria and archaea, also single-celled microorganisms but with an evolutionary history different from that of bacteria, have the enzymes required for its synthesis. Many foods are, however, a natural source of vitamin B12 because of bacterial symbiosis.

Daily requirements were originally estimated at 2–3 µg quantities largely provided by a balanced diet.27 Later studies show that vitamin B12 levels above 400 pg./ml (295 p mol /l, i.e. double the accepted lower limit of normal) do reduce micronucleus formation in peripheral blood lymphocytes and uracil misincorporation into leukocyte DNA. It has therefore been suggested that the current recommended daily intake for vitamin B12 may be inadequate to ensure genomic stability and that a vitamin B12 intake of 7 µg/day, needed for a plasma level of 400 pg./ml would be more appropriate.

After ingestion of vitamin B12, its dissociation from its carrier proteins by gastric acid and pancreatic secretions is an essential prerequisite for the binding of vitamin B12 to the IF secreted by gastric parietal cells.31–35 The vitamin B12–IF complex then reaches the terminal ileum where, as discussed earlier, absorption of vitamin B12 occurs according to an active and saturable mechanism, involving the specific receptor cub am.

The transport of vitamin B12 in the blood as well as its tissue and hepatic uptake require the presence of trans cobalamins (TCBs). TCB types I (TCB I) and III (TCB III) ensure the binding of ~80% of circulating vitamin B12; however, TCB type II (TCB II) plays the predominant role in the key processes of tissue and hepatic uptake of vitamin B12.

Clinically, measuring this active fraction of vitamin B12, bound to TCB II is ensured by the determination of holotranscobalamin.

Holotranscobalamin II is composed of vitamin B12 attached to TCB II, and it represents the biologically active fraction that can be delivered into all DNA synthesizing cells. Liver storage of vitamin B12 is mediated by endothelial cells, hepatocytes being naturally devoid of TCB II receptors. The enterohepatic cycle (5–7 µg daily) and proximal tubular reabsorption of vitamin B12 help maintain physiological reserves of cobalamin at significant levels (up to 5-year reserves).

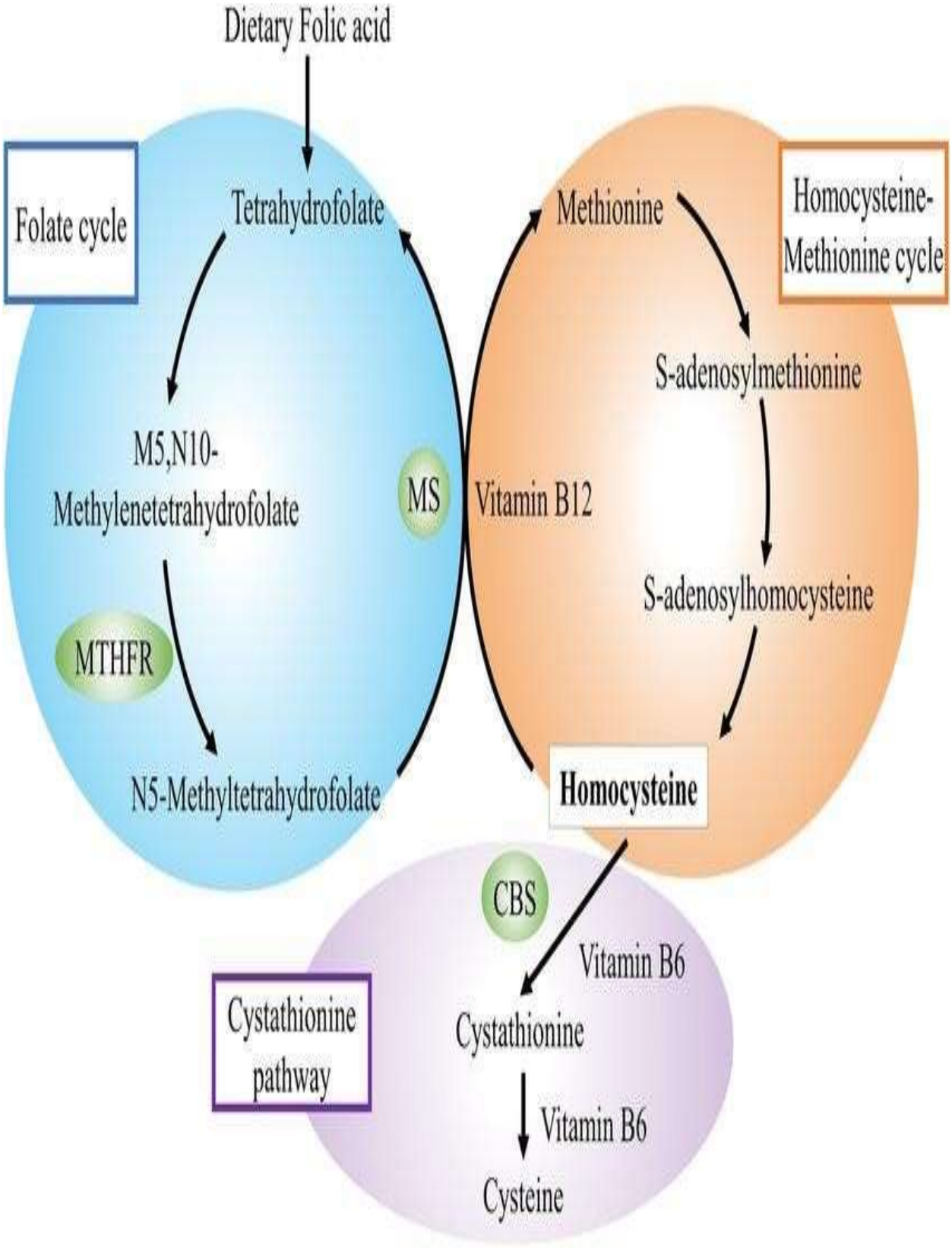


Fig. Metabolism of Vitamin B12

- **Excess vitamin B12 intake:**

Excessive oral intake of vitamin B12 is usually relatively easy to identify in the course of the anamnesis.1 In addition, long-term parenteral administration of vitamin B12 can lead to the development of anti-TCB II autoantibodies, which result in a reduction in TCB II clearance. This induced auto-immunization was observed in 30% of cases in a series of Danish patients treated for pernicious anaemia.

However, in clinical routine, elevated serum cobalamin levels of exogenous origin are encountered primarily in two major situations:

The ingestion by the patient of multivitamin complex tablets containing vitamin B12. This self-medication, sometimes overlooked by the patient, should be systematically investigated at examination, as it is often not spontaneously reported.

Vitamins are micronutrients which are required in your body in small amounts. Vitamins and minerals are essential for normal body

functioning. Therefore, most of us take multivitamin supplements to fulfil our daily requirement of vitamins. If these supplements are taken in an excess, it can lead to vitamin overdose. Similar is the case with vitamin B12 as well. Overdose or excess intake of vitamin B12 can cause certain side effects. The side effects of vitamin B12 depend on the form in which it has been taken

In this article, we will discuss in detail about the common side effects that vitamin B12 overdose can cause along with the daily requirement of vitamin B12 as per your age. Despite its importance, Vitamin B12 deficiency is very common in India. According to statistics, the prevalence Vitamin B12 deficiency in India is as high as 47%, that means, only 26% of the Indian population has sufficient levels of Vitamin B12. Thus, with the increasing cases of vitamin B12 deficiency, the use of vitamin B12 supplements and intake of vitamin B12 rich foods has increased considerably. However, excess of anything has proven to have adverse effects on your body. If you consume too much of vitamin B12 or vitamin B12 supplements, it can lead to an overdose and cause severe health issues.

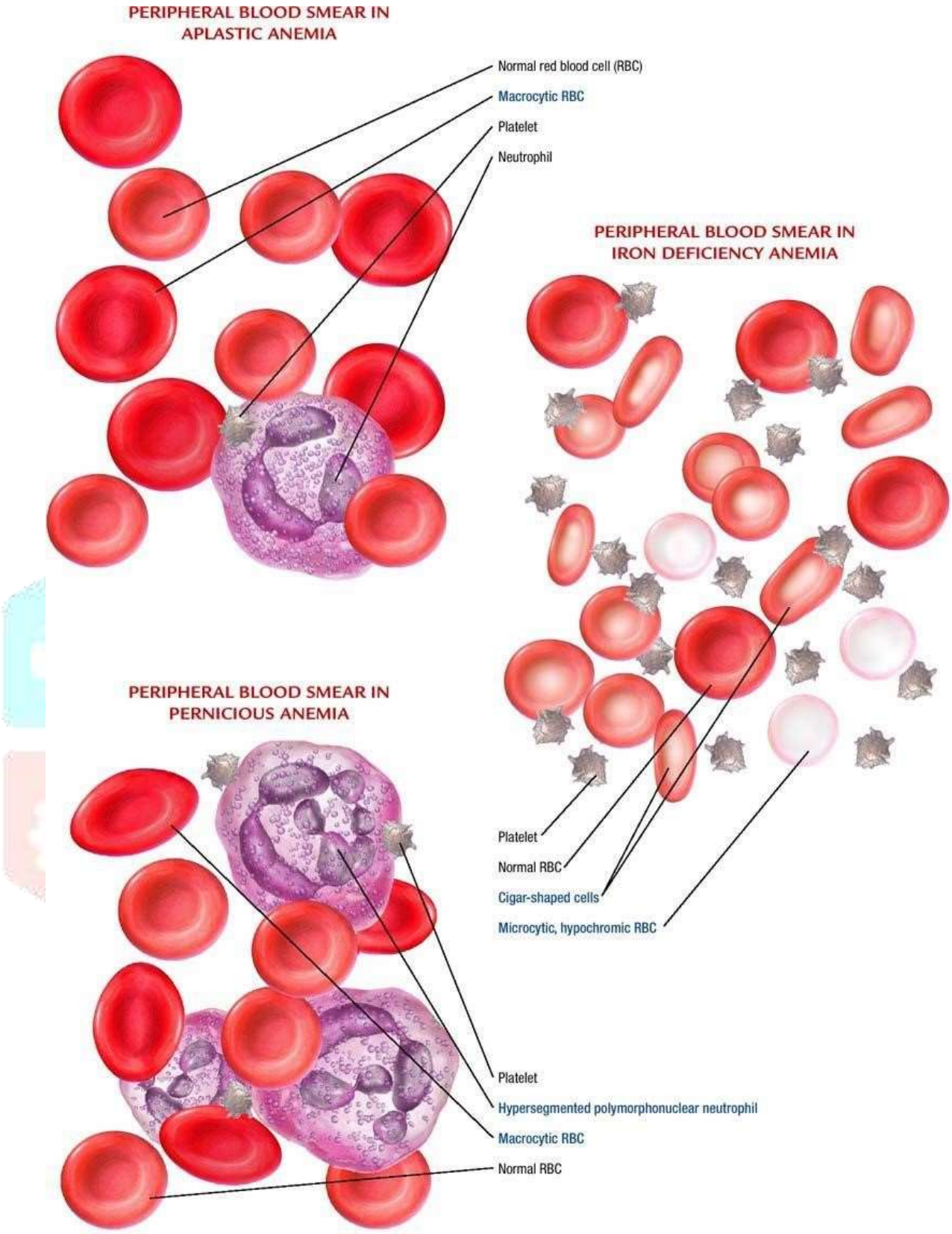


Fig. Type of Anaemia

- **High serum cobalamin and blood disorders**

High serum cobalamin is an anomaly frequently observed in malignant blood diseases and these essentially involve MPDs, including chronic myelomonocytic leukaemia and primary hyper eosinophilic syndrome (HES), myelodysplastic syndromes and acute leukaemia's (ALs), notably promyelocytic leukaemia (AML3)

In ancient literature, high serum cobalamin is included in the biological parameters strongly pointing to a myeloproliferative syndrome including chronic myeloid leukaemia, primary polycythaemia (Vasquez disease), thrombocythemia and other melodiousness.

- **Other causes of high serum cobalamin**

The role of the kidney in the metabolism of vitamin B12 is currently well accepted, albeit not completely understood. Kidney failure is among the causes to look for when confronted with high serum cobalamin. The suggested mechanism is serum accumulation of TCBs. In the series of Denville et al., a significant association between high serum cobalamin and interstitial nephropathy has been reported with an OR of This fact was also documented by Carmel. He hypothesized that cellular uptake of cobalamin by the abundant TC II receptors in the kidney may be impaired.

High serum cobalamin is a frequent and underestimated anomaly. Clinically, it can sometimes be paradoxically accompanied by signs of deficiency resulting in a functional deficit linked to qualitative anomalies, which are related to defects in tissue uptake and action of vitamin B12.

The aetiological profile of high serum cobalamin mostly encompasses severe disease entities for which early diagnosis is crucial to prognosis. These entities are essentially comprised of solid neoplasms, hematologic malignancies and liver diseases.

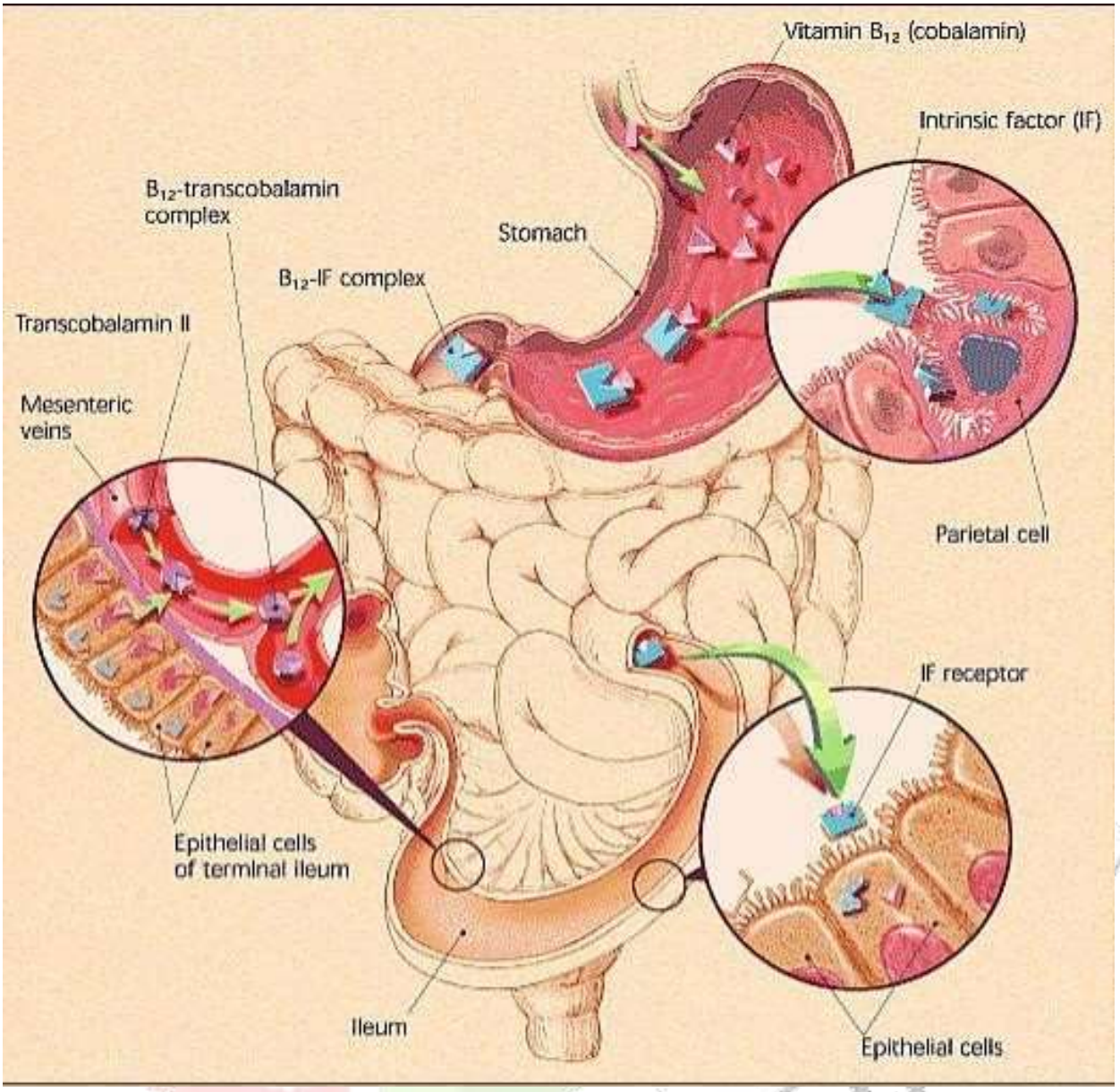


Fig. Excessive intake of vitamin B12)

- **Dietary recommendations:**

Some research shows that most people in the United States and the United Kingdom consume sufficient vitamin B12. However, other research suggests that the proportion of people with low or marginal levels of vitamin B12 is up to 40% in the Western world. Grain-based foods can be fortified by having the vitamin added to them. Vitamin B12 supplements are available as single or multivitamin tablets. Pharmaceutical preparations of vitamin B12 may be given by intramuscular injection. Since there are few non-animal sources of the vitamin, vegans are advised to consume a dietary supplement or fortified foods for B12 intake, or risk serious health consequences. Children in some regions of developing countries are at particular risk due to increased requirements during growth coupled with diets low in animal sourced foods.

The US National Academy of Medicine updated estimated average requirements (EARs) and recommended dietary allowances (RDAs) for vitamin B12 in 1998. The EAR for vitamin B12 for women and men ages 14 and up is 2.0 go/day; the RDA is 2.4 go/d.

RDA is higher than EAR so as to identify amounts that will cover people with higher-than-average requirements. RDA for pregnancy equals 2.6 mg./day. RDA for lactation equals 2.8 mg. /d. For infants up to 12 months the adequate intake (AI) is 0.4–0.5 mg. /day. (AIs are established when there is insufficient information to determine EARs and RDAs.) For children ages 1–13 years the RDA increases with age from 0.9 to 1.8 mg./day.

Because 10 to 30 percent of older people may be unable to effectively absorb vitamin B12 naturally occurring in foods, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with vitamin B12 or a supplement containing vitamin B12. As for safety, tolerable upper intake levels (known as ULs) are set for vitamins and minerals when evidence is sufficient. In the case of vitamin B12 there is no UL, as there is no human data for adverse effects from high doses. Collectively the EARs, RDAs, AIs and ULs are referred to as dietary reference intakes (DRIs).

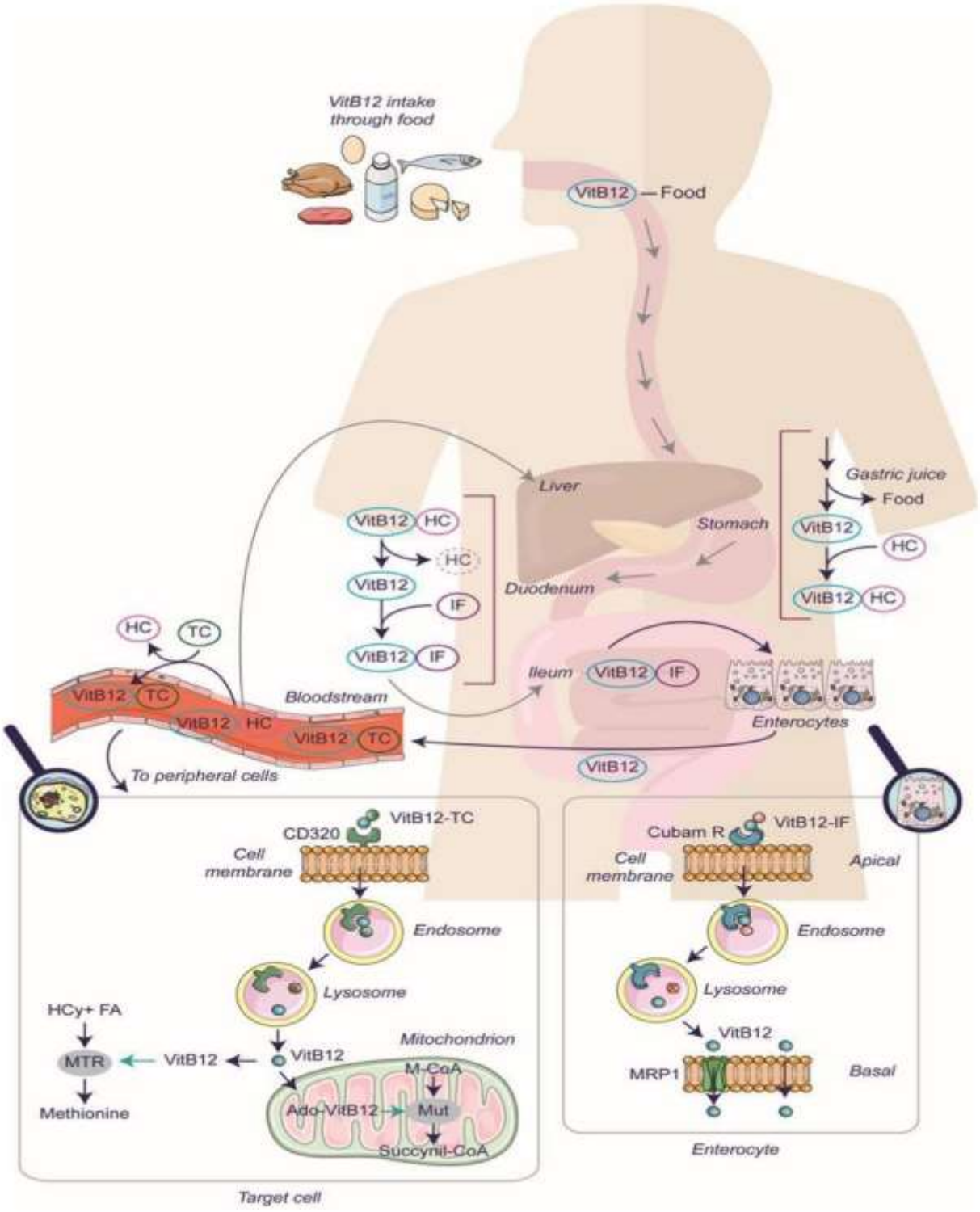


Fig. Dietary recommendations

Source:

- Bacteria and archaea
- Animal -derived foods
- Fortified foods
- supplements

1.Bacterial and archaea

Vitamin B12 is produced in nature by certain bacteria, and archaea. It is synthesized by some bacteria in the gut microbiota in humans and other animals, but it has long been thought that humans cannot absorb this as it is made in the colon, downstream from the small intestine, where the absorption of most nutrients occurs. Ruminants, such as cows and sheep, are foregut fermenters, meaning that plant food undergoes microbial fermentation in the rumen before entering the true stomach (abomasum), and thus they are absorbing vitamin B12 produced by bacteria.

Other mammalian species (examples: rabbits, pikas, beaver, guinea pigs) consume high-fibre plants.

2. Animal-Derived foods

Animals store vitamin B_{12} from their diets in their livers and muscles and some pass the vitamin into their eggs and milk. Meat, liver, eggs and milk are therefore sources of the vitamin for other animals, including humans. For humans, the bioavailability from eggs is less than 9%, compared to 40% to 60% from fish, fowl and meat Insects are a source of B_{12} for animals (including other insects and humans). Animal-derived food sources with a high concentration of vitamin B_{12} include liver and other organ meats from lamb, veal, beef, and turkey; also shellfish and crab meat.

3. Plant and Algae

There is some evidence that bacterial fermentation of plant foods and symbiotic relationships between algae and bacteria can provide vitamin B_{12}. However, the Academy of Nutrition and Dietetics considers plant and algae sources "unreliable", stating that vegans should turn to fortified foods and supplements instead, Natural plant and algae sources of vitamin B_{12} include fermented plant foods such as tempeh and seaweed derived foods such as nori and laverbread. Methyl cobalamin has been identified in *Chlorella vulgaris*.

4. Fortified foods

Foods for which vitamin B12-fortified versions are available include breakfast cereals, plant-derived milk substitutes such as soy milk and oat milk, energy bars, and nutritional yeast. The fortification ingredient is Cyanocobalamin. Microbial fermentation yields adenosyl cobalamin, which is then converted to Cyanocobalamin by addition of potassium cyanide or thiocyanate in the presence of sodium nitrite and heat.

5. Supplement's

Vitamin B_{12} is included in multivitamin pills; in some countries grain-based foods such as bread and pasta are fortified with B_{12}. In the US, non-prescription products can be purchased providing up to 5,000 µg each, and it is a common ingredient in energy drinks and energy shots, usually at many times the recommended dietary allowance of B_{12}.

The vitamin can also be supplied on prescription and delivered via injection or other means.

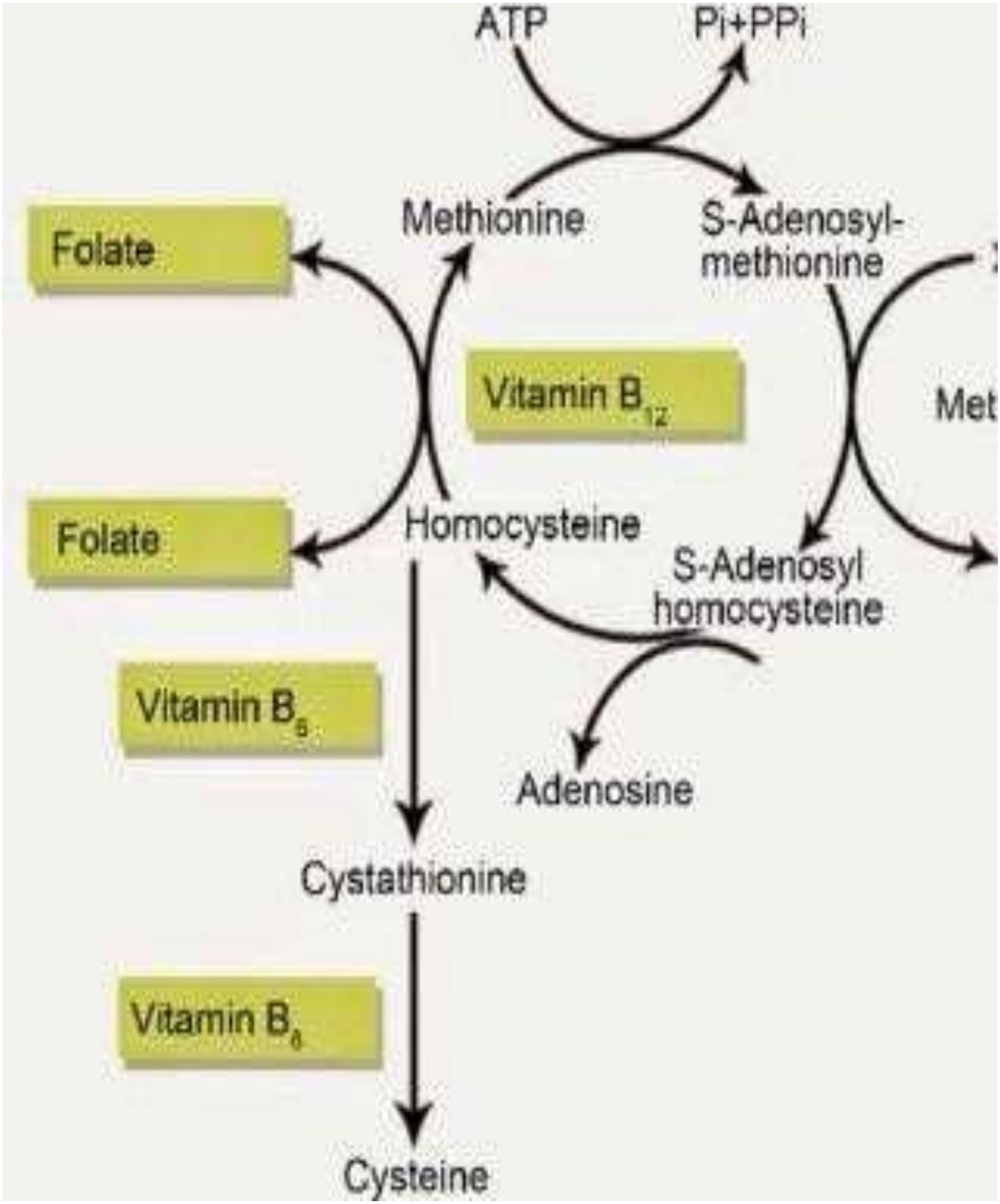

Benefits of B12 Supplementation:
Can increase B12 levels to treat a deficiency
Can reduce homocysteine levels
May benefit those with depression
Supports brain health

Conclusion:

Vitamin B12 might help protect against chronic disease and neural tube defects, but more research, particularly in the area of nutritional genomics, is needed to determine how vitamin B12 might augment the benefits of folic acid. Some consideration should be given to the potential value of fortifying foods with vitamin B12 in addition to the current mandatory folic acid fortification of grains.

Vitamin B12 is essential for our body to function properly. By ensuring an adequate intake of vitamin B12 through their diets, most people can avoid experiencing a deficiency. If you have potential causes for developing a Vitamin B12 deficiency or are experiencing symptoms, it is important to consult a doctor and undergo a blood test to evaluate your levels.

Vitamin B12 is one of the most essential vitamins needed for a health body, so you must ensure you include rich nutrient sources in your diet. The answer to how long to recover from vitamin B12 deficiency depends on how early you can diagnose the condition and get the appropriate treatment. Getting regular blood and other diagnostic tests like CBC done helps in the early detection of this condition.


ATP
Pi+PPi
Methionine
S-Adenosyl-
methionine
Folate
Vitamin B_{12}
Met
Folate
Homocysteine
S-Adenosyl
homocysteine
Vitamin B_6
Adenosine
Cystathionine
Vitamin B_6
Cysteine

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